The State of Rare Disease Drug Development: An FDA Perspective

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Current Priorities at CDER

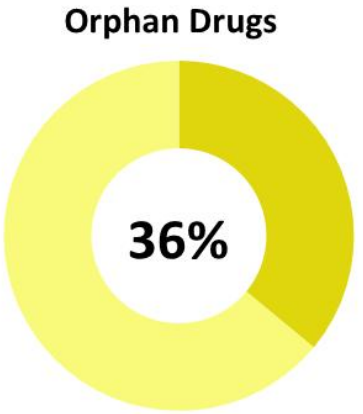
- FDASIA
  - **Expedited reviews and Breakthrough**
  - **Rare diseases**
  - Antibiotic development
  - **Drug shortage**
  - GDUFA goals
  - Electronic submissions
- **Patient Centered Drug Development**
- New Legislation ie Pharmacy Compounding/Track and Trace
- **Rethinking Pharmaceutical Quality**
- Improve Drug Labels
- Drug Safety: Sentinel/IMEDS
- PDUFA V goals
- Build an IT infrastructure that will support these goals

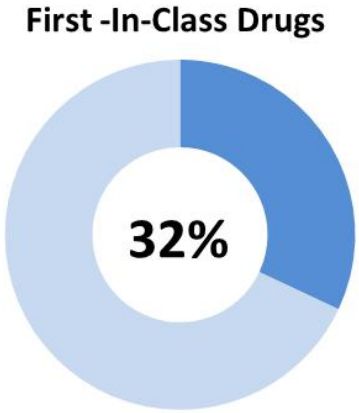
2013 Continues A Strong Track Record For Drug Innovation In The U.S.

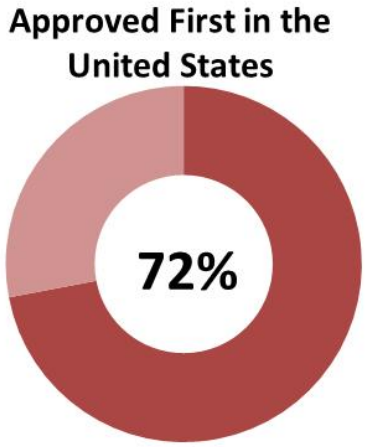
- More than a third (36%) of novel drugs approved to date in CY13 are for rare diseases

Nearly one out of three (32%) of novel drugs approved to date in CY13 are the first in their class

Approximately three-quarters (72%) of novel drugs approved to date in CY13 were first approved in the U.S.

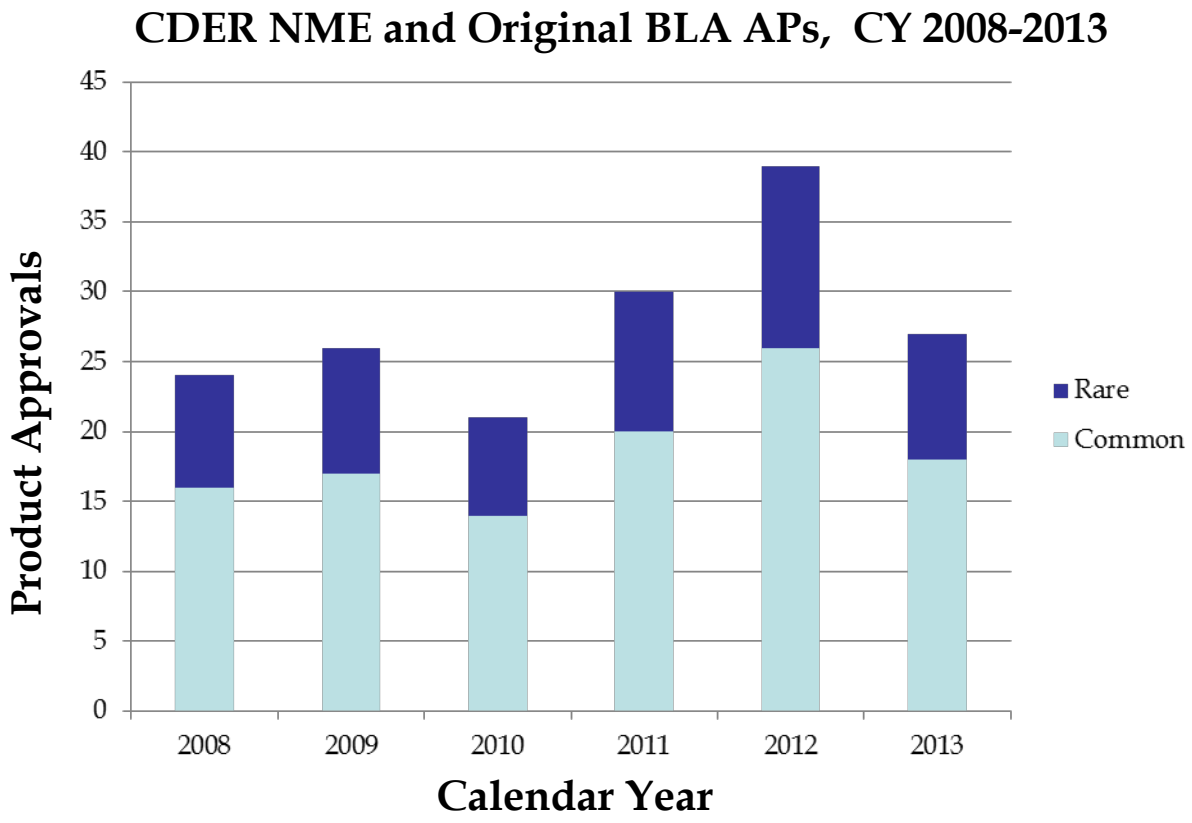






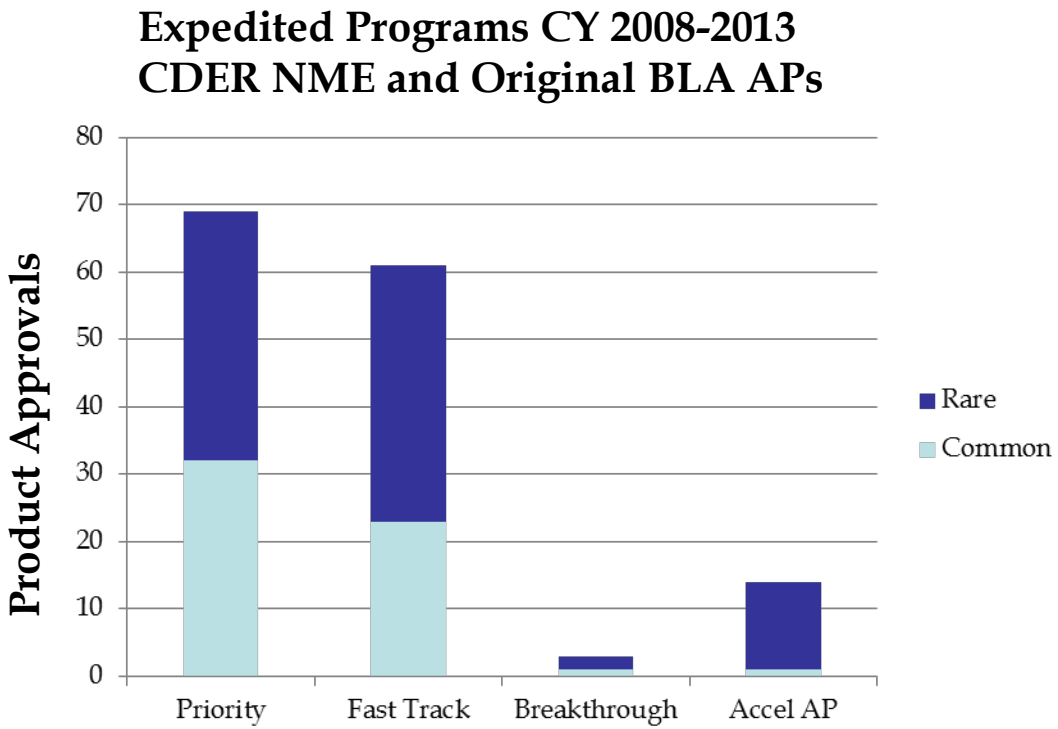
CDER:
Rare Disease Novel Product History

- CY2008-2013* (*as of December 6, 2013)
  - Rare diseases ~1/3 of NME and original biologic APs at CDER



CDER: Expedited Programs

- Rare Diseases
  - Most are serious or life-threatening, unmet medical needs
  - Most qualify for at least one expedited program
    - Many qualify for >1 (almost all for incentives)
    - Rare>>common diseases for expedited programs



Targeted Therapies

- Considered targeted therapy if patients identified for inclusion/exclusion in pivotal trials or for drug use in labeled indication based on a genetic test, biomarker or susceptibility test (e.g., bacterial resistance, tumor genetic mutation)
- Recent analysis of approved NMES and original biological products from 2010-2013, n=121

CDER NME/BLA Approvals 2010-2013*

	Targeted	Non-Targeted
Rare, n=42 (%)	23 (55)	19 (45)
Common, n=79 (%)	11 (14)	68 (86)
Total, n=121 (%)	34 (28)	87 (72)

*As of December 6, 2013

Targeted APs Increasing Over Time

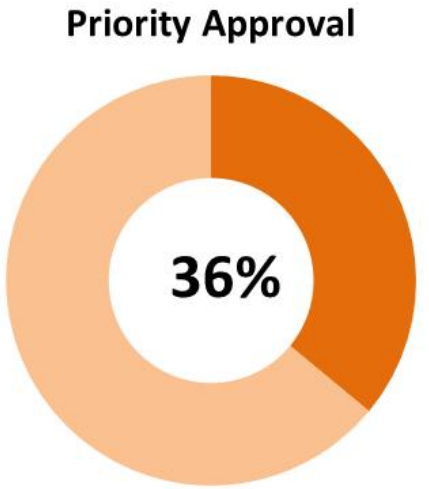
CDER Targeted Therapy NME/BLA Approvals

	Targeted Therapies, % of Total		
Year	All	Rare	Common
1990-1992	~8%	~30%	~2%
2000-2002	~10%	~45%	~5%
2010-2012	~25%	~50%	~10%
2013*	~45%	~80%	~30%

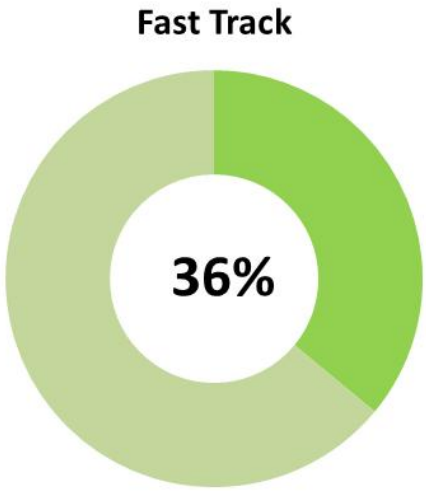
*Jan 1-Dec 6, 2013

CDER Pays Attention That Novel Drugs Receive Expedited Review

- 9 out of 25 (36%) novel drugs approved to date in CY13 were approved under Priority Review



- 9 out of 25 (36%) novel drugs approved to date in CY13 received Fast Track designation



Expedited Review

- Draft guidance recently provided for expedited approvals addressing serious diseases with unmet needs (June '13)
  - Fast track
  - Accelerated Approval
  - Priority Review
  - Breakthrough
    - New designation established by FDASIA that expedites the development and review of drugs that—
    - treat serious/life-threatening disease; and
    - preliminary clinical evidence indicates that drug may demonstrate substantial improvement over existing therapies on ≥ 1 clinically significant endpoints

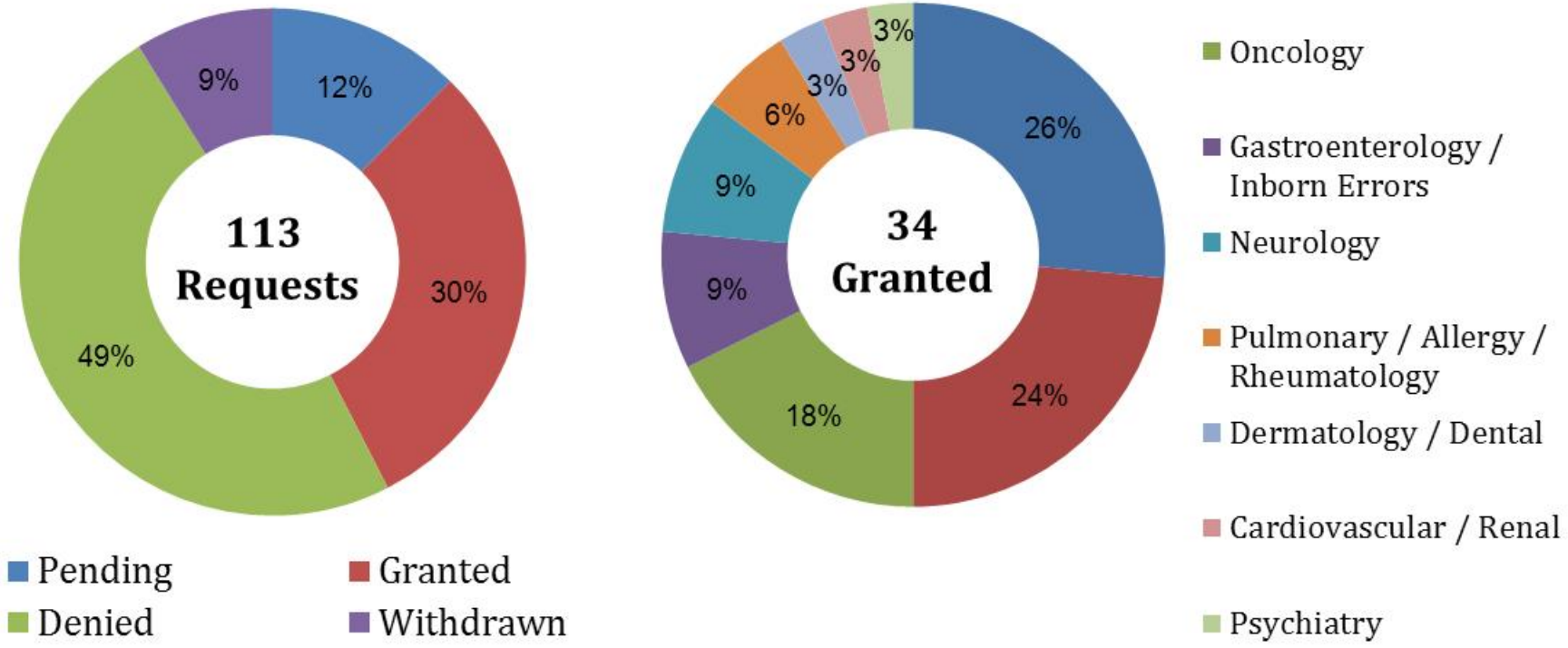
Breakthrough therapy

- Features of breakthrough therapy designation include:
  - Frequent FDA/sponsor communications & meetings
  - Cross-disciplinary project lead assigned to FDA review team to facilitate efficient review and serve as the scientific liaison
  - Organizational commitment involving FDA senior managers and experienced FDA review staff in a proactive collaborative, cross-disciplinary review

- By December
  - 121 requests received
  - 34 granted, about one third for genetic diseases
  - 3 approved already, 2 were for rare diseases

*11/22/13

CDER Has Granted 34 Breakthrough Therapy Designations Since Inception



Data as of 11/30/2013

Breakthrough Therapies: Lessons Learned To Date

- All BT requests in CDER are reviewed by the Medical Policy Council to ensure consistency of standards and approach

- Some designated drugs have been late in development; in some cases the marketing application already submitted
  - Main focus of program is on identifying drugs early in development

- Clinical development often NOT the rate-limiting step
  - Manufacturing development and scale-up must be accelerated

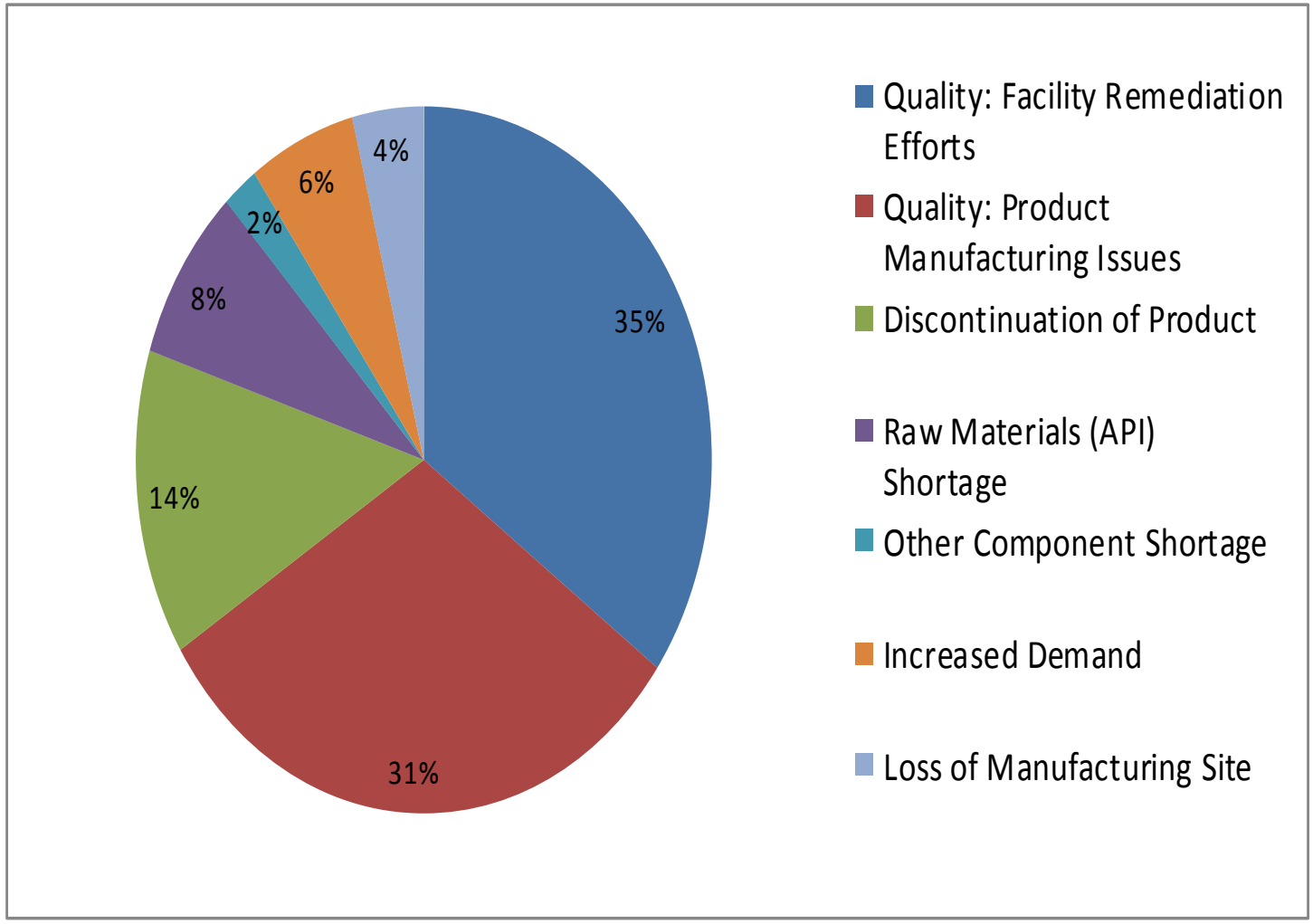
- Program commitments are resource intensive for FDA
  - Number of requests and designations have exceeded expectations

Breakthrough Therapies: Lessons Learned (2)

- Common reasons for denial of BT requests
  - Evidence does not include clinical data
  - Evidence is too preliminary to be considered reliable; e.g., very small number of patients treated, anecdotal case reports
  - Failure to demonstrate "substantial" improvement over available therapy
  - Reliance on a novel biomarker or surrogate endpoint without sufficient evidence to support benefit to patient
  - Post-hoc analyses of failed studies that identify a subset that may benefit

  - Many represent "the triumph of hope over evidence"

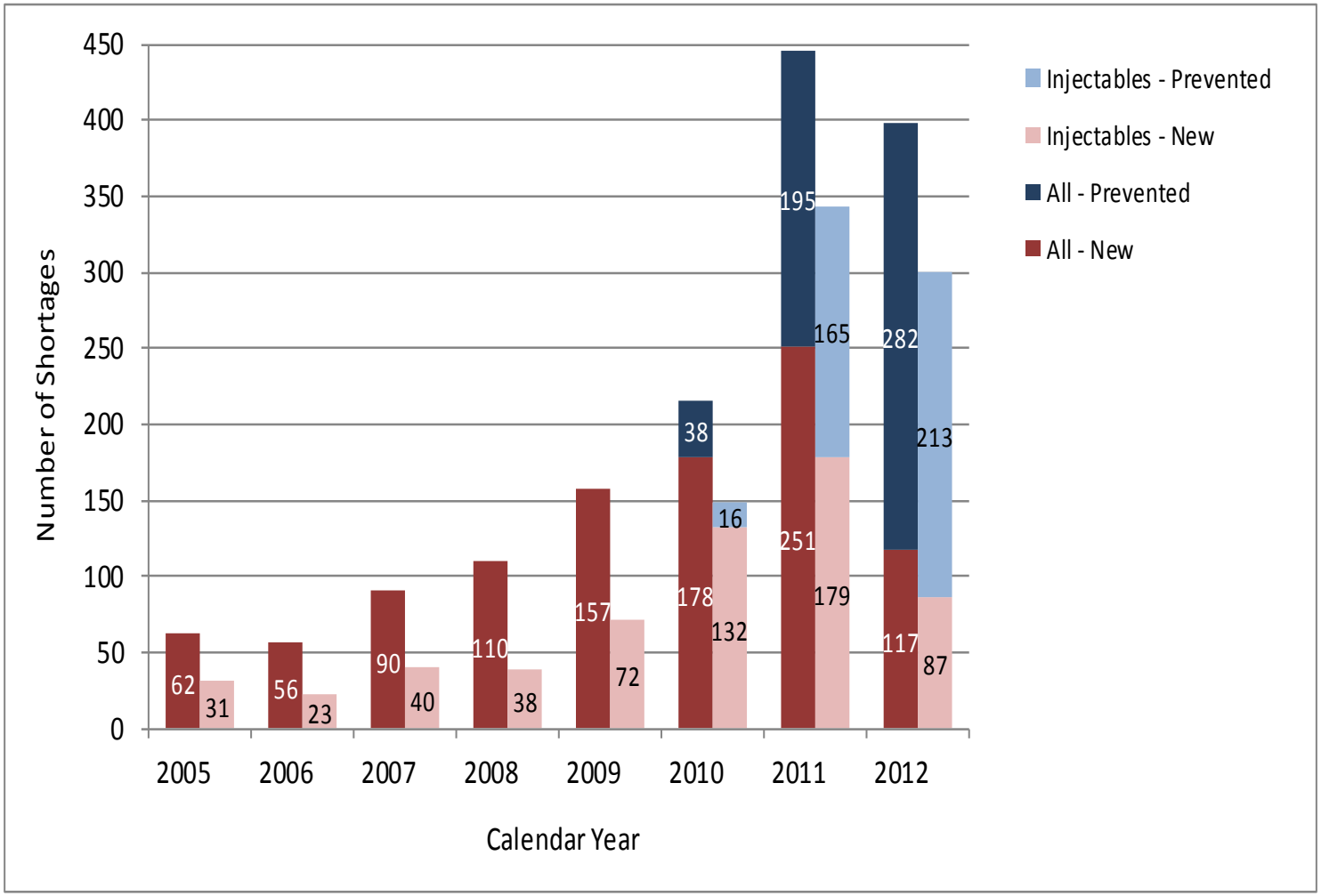
Causes of Drug Shortages: Quality Manufacturing Issues



FDA's Response to Potential Shortage: FDA Actions

- Strategic Plan released October 31, 2013
  - (Presidential directive 2011, FDASIA 2012)
  - **Early Notification** is the key and is required prompt attention
- Perform risk-based analysis to determine ways to address shortage
  - Determine if other manufacturers can increase production
  - Expedite inspections and reviews of submissions
  - Exercise temporary enforcement discretion for new sources of medically necessary drugs
  - Work with the manufacturer to ensure adequate investigation into the root cause of the shortage
  - Review possible risk mitigation measures for remaining inventory
- Communicate effectively to stakeholders
- Long term: Improve manufacturing quality (OPQ)

Value of Early Notification:



Proposed Office of Pharmaceutical Quality: Principles

- **Put patients first** by balancing risk and availability.
- Have one quality voice by integrating review and inspection across product lifecycle.
- Safeguard clinical performance by establishing scientifically-sound and clinically relevant quality standards.
- Maximize focus and efficiency by applying risk-based approaches.
- Encourage innovation by advancing new technology and manufacturing science.
- Put Quality over Compliance
- Attention on how well drugs are manufactured
- Metrics, ie lot failure
- Create an ability to examine Quality across the industry

Patient-Focused Drug Development under PDUFA V

- FDA's drug benefit-risk assessment considers severity of disease condition and degree of unmet medical need— clinical context
  - Patients are uniquely positioned to inform FDA understanding of the clinical context
- Patient-Focused Drug Development is part of FDA commitments under PDUFA V
  - Convene at least 20 meetings on specific disease areas
  - Patient perspective helps inform our understanding of the context for the assessment of benefit-risk and decision making for new drugs
  - Input can inform FDA analysis both during and outside of review
  - 2013 meetings included narcolepsy and muscular dystrophy
  - Feedback has been good

Disease areas to be the focus of meetings for FY 2014-2015

FY 2014 – 2015

- Alpha-1 antitrypsin deficiency
- Breast cancer
- Chronic Chagas disease
- Female sexual dysfunction
- Fibromyalgia
- Hemophilia A, Hemophilia B, von Willebrand disease, and other heritable bleeding disorders
- Idiopathic pulmonary fibrosis
- Irritable bowel syndrome, gastroparesis, and gastroesophageal reflux disease with persistent regurgitation symptoms on proton-pump inhibitors
- Neurological manifestations of inborn errors of metabolism
- Parkinson's disease and Huntington's disease
- Pulmonary arterial hypertension
- Sickle cell disease

Pediatric Rare Disease Voucher Program

- FDASIA
- FDA will award priority review voucher to sponsors of rare pediatric disease product application that meet certain criteria
  - Prevalence predominantly pediatric
  - New drug
  - Not seeking adult indication
- Can seek designation during development
- Voucher is transferable
- Formal guidance to be published

Regulatory Collaborations

- Enhanced international collaborations in recent years
- EU:
  - International Rare Disease research Consortium (IRDIRC)
    - Several FDA members participate
  - Harmonized orphan drug application form
  - Regular meetings on orphan drugs, cancer, and pediatrics

- NIH
  - CDER-NIH CC taskforce
  - IND regulatory training workshop

Rare Disease Priorities

- Significant percentage of novel product approvals
  - Trend expected to increase
- High use of expedited pathways and incentive programs
- Targeted therapies increasingly common in drug development
  - Common disease subsets → "orphan subsets"[1]
    - E.g., BRAF V600 mutation subsets of melanoma
  - Rare Diseases and Rare Disease subsets
    - E.g., Cystic Fibrosis *G551D* mutation subset
  - Smaller subsets available for clinical trials, smaller clinical development programs
  - Larger magnitude of effects anticipated
    - Safety, R-B assessments
  - Need for flexibility, novel trial designs, translational science development

[1]FR Notice, Docket No. FDA-2011-N-0583, Vol. 78 (113). Orphan Drug Regulations Final rule. June 12, 2013

Summary

- CDER initiatives in drug shortages, pharmaceutical quality, expedited reviews, pediatric rare disease vouchers, and patient informed decision making should have a significant impact on rare disease drug development.
- Rare Diseases have always been a leader in innovation and continue to do so.

Addendum

Snapshot of CY 2013
NME NDAs/BLAs† Drug Approvals (1/2)

Trade Name	Met PDUFA Goal Date*	Approved on First Cycle	Priority Approval	Fast Track	First in Class	Approved First in the U.S.	Orphan Drug	Breakthrough Therapy
NESINA								
KYNAMRO								
POMALYST								
KADCYLA								
OSPHENA								
LYMPHOSEEK								
DOTAREM								
TECFIDERA								
INVOKANA								
BREO ELLIPTA								
XOFIGO								
TAFINLAR								
MEKINIST								

Data as of 11/30/2013

† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient an d combinations) are only counted once. Therefore, the numbers represented here for FY13 filings are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded

*A PDUFA Goal Date is marked as met if the NME is acted upon within its approval cycle due date

Snapshot of CY 2013
NME NDAs/BLAs† Drug Approvals (2/2)

Trade Name	Met PDUFA Goal Date*	Approved on First Cycle	Priority Approval	Fast Track	First in Class	Approved First in the U.S.	Orphan Drug	Breakthrough Therapy
GILOTRIF								
TIVICAY								
BRINTELLIX								
DUAVEE								
ADEMPAS								
OPSUMIT								
VIZAMYL								
GAZYVA								
APITOM								
IMBRUVICA								
LUZU								
OLYSIO								

Data as of 11/30/2013

† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for FY13 filings are not indicative of workload in the PDUFA V Program.

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* A PDUFA Goal Date is marked as met if the NME is acted upon within its approval cycle due date